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(54) Title: COMBINATIONS FOR HORMONE REPLACEMENT THERAPY CONTAINING A NATURAL OESTROGEN, A NATURAL PROGESTOGEN AND A NATURAL ANDROGEN

(57) Abstract

The invention provides the use of a natural oestrogen, a natural progestogen and a natural androgen as a combined preparation for simultaneous, separate or sequential use in the treatment of menopausal or post-menopausal disorders in women. Preferably, the use is simultaneous administration of a mixture of oestradiol, progesterone and testosterone.

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COMBINATIONS FOR HORMONE REPLACEMENT THERAPY CONTAINING A NATURAL OESTROGEN, A NATURAL PROGESTOGEN AND A NATURAL ANDROGEN

The present invention relates to the use of a combination of hormones in the treatment of menopausal or post-menopausal disorders in women.

The value of natural oestrogens as hormone replacement therapy for post-menopausal women is well established. After the menopause the ovarian production of oestradiol falls markedly. Replacement of oestrogens has been shown to alleviate menopausal symptoms such as hot flushes and vaginal dryness, depression, and skin changes. It is also known to protect against osteoporosis and cardiovascular disease. Preliminary research also suggests protection against pre-senile dementia.

Oestrogen replacement therapy, although beneficial in many ways, has one serious side effect with important implications: oestrogen tends to cause stimulation of the endometrium. Before the menopause, this tendency is opposed by another hormone of the ovarian endocrine cycle, namely progesterone. The interaction between the effects of these two hormones leads to the endometrium being repeatedly stimulated and then shed in a monthly cycle with no net thickening. If prolonged oestrogen replacement therapy is taken in the absence of progesterone or a substance with progesterone-like activity, known as a progestogen, the oestrogen will cause unopposed stimulation of the endometrium which may eventually develop into cancer.

For this reason oestrogen replacement therapy for women with a uterus is usually offered as oestrogen together with a synthetic progestogen. Progestogens may be natural or synthetic. The natural progestogens include progesterone and pregnenolone which are not orally active, and therefore are not offered in conventional medical practice as

progestogenic oppositions for oestrogen replacement therapy. There are only two products listed in the British National Formulary under "progesterone". These are a pessary for administration *per vaginum* or *per rectum* (Cyclogest®, Hoechst) and an intramuscular injection (Gestone®, Ferring). The two products are indicated for prevention of recurrent miscarriage, progesterone being a pro-gestational hormone.

Pharmaceutical interest and data production is, and has been, sharply focused towards the development of synthetic orally active progestogens for use in the combined contraceptive pill. These include the progesterone analogues dehydrogesterone, hydroxyprogesterone and medroxyprogesterone, and the testosterone analogues norethisterone and norgestrel and their derivatives.

Synthetic progestogens are described as anectodally as "a necessary evil". They are taken to prevent endometrial cancer, but the concern is that they may act to antagonise the beneficial effects of oestrogen replacement therapy, for example by altering serum lipids to increase the risk of cardiovascular disease. Furthermore, they often produce unacceptable side effects such as abdominal bloating, breast tenderness, headaches, hair loss, emotional lability or breakthrough bleeding. Different progestogens have different side effect profiles, but it is not uncommon that an individual woman cannot find an acceptable progestogen and chooses to undergo major surgery in the form of a hysterectomy so that she can continue to take oestrogen replacement therapy without the need for progestogenic opposition. Others may choose not to take their prescribed progestogen whilst continuing with oestrogen replacement therapy and thereby risking the development of endometrial cancer. It has been found in practice that more than 20% of women will stop hormone replacement therapy, despite its benefits, within nine months of commencing treatment, major reasons for this being the progestogenic side effects and dislike of continuing to menstruate.

Oestrogens and progestogens may be taken as tablets. For women with a uterus, the oestrogen tablet is taken every day with the addition of a tablet of progestogen for seven to ten days each month to provoke a menstrual bleed. For older postmenopausal women there also exist some tablets containing both oestrogen and progestogen in combination which are taken daily in the hope of avoiding the monthly bleed. Many women have major problems with break-through bleeding together with other progestogenic side effects.

Patches usually contain oestrogen alone but may also contain progestogen. They are applied to the buttock or arm and changed once or twice a week. The advantage over tablets is that the hormone is absorbed transdermally, therefore avoiding the so-called "first pass effect" of hormones passing through the liver on the way from the gut to the systemic circulation and thereby activating liver enzymes and altering blood lipids. The disadvantage of patches is that they are unsightly, often cause a local irritation at the site of application and tend to fall off in hot weather.

Implants are tiny pellets of oestradiol or testosterone which are inserted by a doctor, every six months, under the skin of the anterior abdominal wall or the buttock. Their advantage is the improved compliance; their disadvantage that if the treatment is unacceptable it can be very difficult to remove the implant. Further some women develop reduced sensitivity to the extremely high serum levels of oestradiol achieved. This results in the onset of menopausal symptoms as serum levels fall despite serum levels of oestradiol which are within the therapeutic range.

Gels and creams are becoming more popular. Oestradiol is produced in gel form (Oestrogel®, Hoechst; Sandrena®, Orgaron). A metered dose is applied daily to the upper arms or thighs and rubbed in. It presents all the advantages of avoiding the first pass effect whilst not needing to wear an

unsightly patch or undergo a minor surgical procedure every six months. There is also a cream available in the UK which contains natural progesterone (Pro-Gest®, Transitions/Higher Nature) although it is not widely prescribed.

Unlike the synthetic progestogens, progesterone is not currently indicated for use in combination with oestrogen for hormone replacement therapy. Magos A.L. and Studd J.W.W. in Progress in Obstetrics and Gynaecology, Vol. 8, pages 313-334 (J.W.W. Studd Ed.) found that a combination of progesterone with oestradiol resulted in irregular breakthrough bleeding. J.C. Montgomery and D. Crook in HRT and Osteoporosis, J. Drife and J.W.W. Studd Eds. Springer-Verlag, London, 1990, report that progesterone in doses high enough to prevent endometrial hyperplasia is associated with unacceptable drowsiness due to the action of progesterone as a central nervous system depressant. In discussions of endometrial opposition, natural progesterone is often confused with the synthetic progestogens. Important differences in their chemical structure which could lead to different actions and side effect profiles have not been considered.

Dr. J.R. Lee is a physician in the United States who has lectured widely and written two books (Natural Progesterone, the Multiple Roles of a Remarkable Hormone and What your Doctor may not tell you about Menopause - the Breakthrough Book on Natural Progesterone). These books allege a wide variety of beneficial effects of natural progesterone, but also contest the beneficial effects of oestrogen. They discount the evidence which supports the use of oestrogen, and they do not propose a combination therapy. Indeed, they suggest that oestrogen is used to excess and is thus responsible for most gynaecological complaints.

The androgens, which include testosterone, androstenedione and dehydroepiandrosterone, are considered to be male hormones, although they are also produced by the ovaries.

Testosterone is not commonly offered in preparation of hormone replacement therapy for women. There is a concern that supplementation of women with this male hormone may have an adverse effect on their risk of cardiovascular disease. Testosterone is also not indicated for women because of the possibility of masculinising side effects, such as facial hair and acne. However, J.W.W. Studd, W.P. Collins and J.R. Newton in Journal of Obstetrics and Gynaecology, Vol.84, pages 314-315 (1977), have suggested that testosterone may have a valuable role for some women in improving libido after the menopause.

It is an object of the present invention to provide an improved hormone replacement therapy for the treatment of menopausal and post-menopausal disorders in women.

It has been found, surprisingly, that a hormone replacement therapy comprising a combination of natural oestrogens, progestogens and androgens provides beneficial synergistic effects.

Accordingly, the present invention provides the use of a natural oestrogen, a natural progestogen and a natural androgen as a combined preparation for simultaneous, separate or sequential use in the treatment of menopausal or post-menopausal disorders in women.

Preferably, the natural oestrogen is selected from the group consisting of oestradiol, oestrone, oestriol and mixtures thereof. Preferably, the natural progestogen is selected from the group consisting of progesterone, pregnenolone and mixtures thereof. Preferably, the natural androgen is selected from the group consisting of testosterone, androstenedione, dehydroepiandrosterone (DHEA) and mixtures thereof. More preferably, the natural oestrogen consists essentially of oestradiol, the natural progestogen consists essentially of progesterone, and the natural androgen consists essentially of testosterone.

The combined preparation used in the present invention preferably has the natural oestrogen, natural progestogen and natural androgen in admixture with a suitable pharmaceutical excipient for simultaneous administration of all three hormones. The combined preparation can be adapted for oral, transdermal (patch, cream or gel), subcutaneous implant, vaginal, rectal or parenteral administration. Preferred formats are those already used for HRT and oral contraceptive hormone administration. The combined preparation may, of course, comprise different hormones in different formats for separate or sequential use. For example, the combined preparation could comprise the oestrogen and androgen in oral adminstration format, and the progestogen in a transdermal administration format. The hormones may, of course, be in the form of biologically acceptable prodrugs such as esters for sustained release in vivo.

The hormone concentrations and excipients used in the various combined preparation formats will be similar to those used for the administration of contraceptive hormones to pre-menopausal women, and/or the existing HRT therapies described above. The dosage levels will depend on the bioavailability of the hormones in each given format. For example, there is a well known "first pass" effect with oral administration of these hormones, whereby a substantial fraction of the hormone is initially removed by the liver. Therefore, it is only really practicable to define the present invention in terms of the salivary and serum levels of the hormones that are to be achieved for the duration of the therapy.

Preferably, the use according to the present invention achieves a salivary oestradiol level of 0.5 - 500 pg/ml, more preferably 5 - 300 pg/ml, and most preferably 50 - 300 pg/ml, or a serum oestradiol level of 100 - 1650 pmol/liter, more preferably 250 - 1,650 pmol/liter.

Preferably, the use according to the present invention achieves a serum oestrone level of from 5 - 50 μmol/liter, more preferably 10 - 50 μmol/liter, or a salivary oestrone level of 30 to 90 pmol/liter.

Preferably, the use according to the present invention achieves a serum oestriol level of from 1 - 1,000 μmol/liter, preferably 10 - 1,000 μmol/liter and most preferably 100 - 800 μmol/liter, or a salivary oestriol level of from 1 to 10 nmol/liter.

Preferably, the use according to the present invention achieves a serum testosterone level of from 0.1 to 30 nmol/liter or a salivary testosterone level of from 18 - 140 pg/ml, more preferably 30 - 140 pg/ml, and most preferably 50 - 80 pg/ml.

Preferably, the use according to the present invention achieves a salivary dehydroepiandrosterone (DHEA) level of from 40 - 300 pg/ml, more preferably 100 - 300 pg/ml. The serum DHEA sulfate level is preferably 1 - 120 μmol/liter, more preferably 5 - 100 μmol/liter.

Preferably, the use according to the present invention achieves a serum level of androstenedione in the range of 4 - 100 nmol/liter, preferably 5 -50 nmol/liter.

The salivary hormone levels defined above are determined using kits from Aeron Life Cycles Laboratories, California. The kits are FDA approved radioimmunoassay kits.

Further radioimmunoassay procedures for determination of these hormones in saliva are described in the following references, the entire contents of which are hereby incorporated by reference:-

Huang N.H., Dill B., Besch P.K., Hinkley Radioimmunoassay

of uncongugated estriol in saliva. Clin. Chem. 27:1080; (1981);

Walker R.F., Wilson D.W., Read G.F., Riad-Fahmy D 1980 Assessment of testicular function by the radioimmunoassay of testosterone in saliva. Int. J. Androl 3:105; (1980)

Walker R.F., Read G.F., Riad-Fahmy D. Radioimmunoassay of progesterone in saliva application to the assessment of ovarian function. Clin. Chem. 25:2030; (1979);

Luisi M. Silvestri D, Maltini G, Castarsi A.L., Franchi F 1980 Radioimmunoassay of oestrone in male saliva. Lancet 2:542; (1980); and

Chearskul S., Rincon-Rodriguez I., Sofi S.B., Donaldson A. Jeffcote L.S.L., Simple, direct assays for the measurement of estradiol and progesterone in saliva, In: Radioimmunoassay and Related Procedures in Medicine, IAEA, Vienna 1982.

Similar radioimmunoassay or enzyme-linked immunosorbent assay (ELISA) methods may be applied, with minor modification, to the determinations of these hormones in serum. Suitable antibodies for use in the assays are available commercially, for example from Diagnostic Products Corp. (U.K.) and Scheron Diagnostics (U.K.).

The menopausal or post-menopausal disorders that can be treated in accordance with the present invention include: osteopenia and osteoporosis; hypercholesterolaemia, hypertension and atherosclerotic arterial disease; vasomotor instability including hot flushes and night sweats; urogenital atrophy including detrusor instability and stress incontinence; poor libido; skin, hair and nail problems; anxiety, depression and insomnia; memory loss and pre-senile dementia, and mixtures thereof.

It is also envisaged that the combined preparations used in the present invention can also be used for the treatment of certain other hormone related deficiency conditions, including women with premature ovarian failure, Turner's syndrome, testicular feminisation syndrome, sex change, hermaphroditism and pseudohermaphroditism, premenstrual syndrome, addback HRT for use with gonadotropin-releasing hormone analogues for endometriosis, pelvic pain, pelvic venous congestion, and benign breast disease.

Accordingly, in another aspect, this invention provides a method for the treatment of any of the disorders enumerated above, comprising administering to a human patient a therapeutically effective amount of a natural oestrogen, a natural progtestogen and a natural androgen as a combined preparation.

An embodiment of the present invention will now be described further, by way of example, as follows.

Example 1

A clinical study of the effect of administration of a combined preparation in accordance with the present invention was performed as follows.

25 post-menopausal women with intact uteri were recruited. All complained of significant menopausal symptoms including a minimum of moderately severe hot flushes and night sweats, vaginal dryness and poor libido.

They were offered the following treatments: oestradiol, progesterone and testosterone (to three subjects); oestradiol and progesterone only (four subjects); progesterone alone (seven subjects); oestradiol, testosterone and synthetic progestogen (seven subjects); and Org OD 14 (supplied by Organon Corporation under the Registered Trade Mark LIVIAL), a synthetic steroid with weak oestrogenic, progestrogenic and central effect (four

subjects).

The oestradiol, progesterone and testosterone were administered in conventional formats, the quantities of each being titrated to achieve the following serum levels: Oestradiol 300-1000 pmol/liter; progesterone 5-50 nmol/liter; and testosterone 2-4 nmol/liter.

The testosterone serum levels were determined by competitive radioimmunoassay on an ATS 180 automated machine using labelled antibody supplied by Scheron Diagnostics (UK). The oestradiol and progesterone serum levels were determined by automated ELISA on a Boehringer Mannheim ES700 machine using antibody supplied by Diagnostic Products Corp. (UK). The measured between-batch coefficients of variation were: oestradiol 12.5% (at 200 pmol/liter); testosterone 10.8% (at 3.1 nmol/liter); and progesterone 9.2% (at 32 nmol/liter).

Synthetic progestogen was offered as either dydrogesterone 10mg or medroxyprogesterone acetate 5mg taken daily for the first ten days of each calendar month.

The subjects were reviewed after six months of treatment. Any reports of progestogenic side effects or complaints of hot flushes and night sweats, vaginal dryness, poor libido, or unscheduled vaginal bleeding were noted. The results are shown in Table 1.

Table 1

HRT	n	PSE	HF/S	VagD	Lib	VB	ASE(%)
Org OD14	4	++++	+	-	++	+++	100
En&Tn&Ps	7	+++	-	-	-	-	45
Pn only	7	-	++	++	+	-	45
En&PN	4	-	-	-	+	-	25
En&Pn&Tn	-	-	-	-	-	-	0

Key:

HRT type of hormone replacement therapy
n number of subjects
PSE progestogenic side effects
HF/S hot flushes and night sweats
VagD vaginal dryness
Lib loss of libido
VB unscheduled vaginal bleeding
ASE % of subjects experiencing any one or more side effect after six months on the treatment
En natural oestrogen (oestradiol)
Pn Natural progestogen (progesterone)
Ps synthetic progestogen (dydrogesterone, norethisterone or medroxyprogesterone acetate)
Tn natural androgen (testosterone)

From these it results it can be concluded that the combination of a natural oestrogen, natural progestogen and natural androgen affords the greatest relief from menopausal symptoms with minimum adverse side effects.

The above embodiment has been described by way of example only. Many other embodiments falling within the scope of the accompanying claims will be apparent to the skilled reader.

CLAIMS

1. Use of a natural oestrogen, a natural progestogen and a natural androgen as a combined preparation for simultaneous, separate or sequential use in the treatment of menopausal or post-menopausal disorders in women.

2. Use according to claim 1, wherein the natural oestrogen is selected from the group consisting of oestradiol, oestrone, oestriol and mixtures thereof.

3. Use according to claims 1 and 2, wherein the natural progestogen is selected from the group consisting of progesterone, pregnenolone and mixtures thereof.

4. Use according to claims 1, 2 and 3, wherein the natural androgen is selected from the group consisting of testosterone, androstenedione, dehydroepiandrosterone (DHEA) and mixtures thereof.

5. Use according to any preceding claim, wherein the natural oestrogen consists essentially of oestradiol, the natural progestogen consists essentially of progesterone, and the natural androgen consists essentially of testosterone.

6. Use according to any preceding claim, wherein said use achieves a salivary oestradiol level of 0.5 - 300 pg/ml or a serum oestradiol level of 100 μmol/liter - 1,650 μmol/liter.

7. Use according to any preceding claim, wherein said use achieves a salivary oestrone level of 30 to 90 pmol/liter or a serum oestrone level of 5 - 50 micromol/liter.

8. Use according to any preceding claim, wherein said use

achieves a salivary oestrial level of 1 to 10 nmol/liter or a serum oestriol level of 1 - 1,000 micromol/liter.

9. Use according to any preceding claim, wherein said use achieves a salivary testosterone level of from 18 pg/ml to 740 pg/ml or a serum testosterone level of from 0.1 to 30 nmol/liter.

10. Use according to any preceding claim, wherein said use achieves a salivary dehydroepiandrosterone (DHEA) level of from 40 pg/ml to 300 pg/ml or a serum DHEA sulfate level of 1 - 120 micromol/liter.

11. Use according to any preceding claim, wherein said use achieves a serum level of androstenedione of 4 - 100 nmol/liter.

12. Use according to any preceding claim, wherein said combined preparation is a single medicament comprising said natural oestrogen, said natural progestogen and said natural androgen admixed with pharmaceutical excipients for simultaneous administration.

13. Use according to any preceding claim, wherein said combined preparation comprises a patch, cream or gel for transdermal administration.

14. Use according to any preceding claim, wherein said combined preparation comprises a subcutaneous implant.

15. Use according to any preceding claim, wherein said combined preparation comprises a cream, gel or pessary for vaginal administration.

16. Use according to any preceding claim, wherein said menopausal or post-menopausal disorder is selected from the group consisting of osteopenia and osteoporosis;

hypercholesterolaemia, hypertension and atherosclerotic arterial disease; vasomotor instability including hot flushes and night sweats; urogenital atrophy including detrusor instability and stress incontinence; poor libido; skin, hair and nail problems; anxiety, depression and insomnia; memory loss and pre-senile dementia, and mixtures thereof.

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HARGROVE J.T. ET AL: "An alternative method of hormone replacement therapy using the natural sex steroids" INFERTILITY AND REPRODUCTIVE MEDICINE CLINICS OF NORTH AMERICA, 1995, 6/4 (653-674), USA, XP002045938 see page 668, paragraph 1 see table 3 ---	1-16
X	BOUDET J. ET AL: "Study of the epicutaneous kinetic diffusion of a cream containing estrone, estradiol, testosterone and pregnenolone (Fadiamone (R)) in menopausal women" NOUV. DERMATOL., 1994, 13/9 (658-661), FRANCE, XP002045939 see abstract --- -/--	1-16

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

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Name and mailing address of the ISA	Authorized officer
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Inter ...nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ALDEN J.C.: "Osteoporosis - A review" CLIN. THER., 1989, 11/1 (3-14), USA, XP002045940 see page 10, column 2, paragraph 3 - page 11, column 2 ---	1-16
X	FERNANDEZ-GUASTI, ALONSO ET AL: "Synergistic action of estradiol, progesterone and testosterone on rat proceptive behavior" PHYSIOL. BEHAV., 1991, 50, 1007-11, XP002045941 see page 1010, column 2, line 2-5 ------	1-16

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